Accelerating COVID-19 Therapeutic Interventions

122nd Meeting of the Advisory Committee to the Director

H. Clifford Lane, MD
Clinical Director, NIAID, NIH

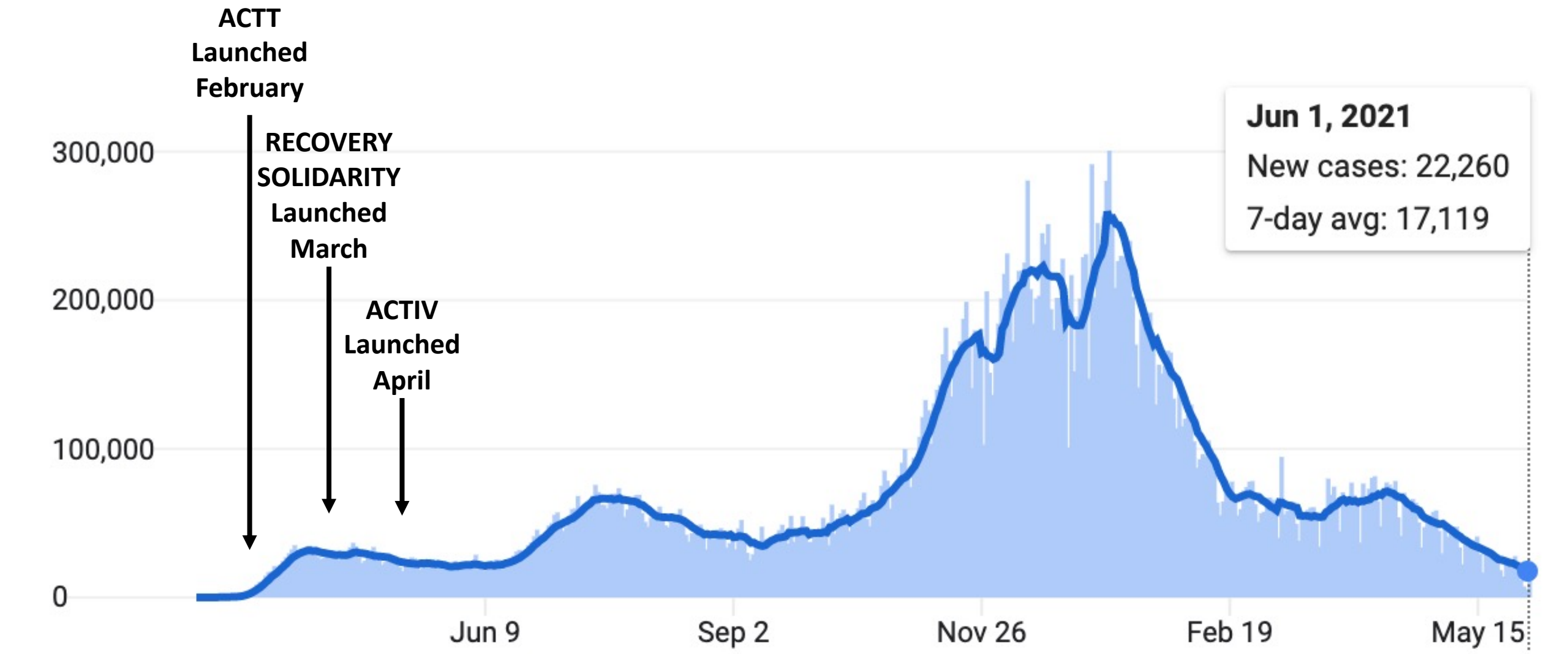
Gary Gibbons, MD
Director, NHLBI

June 10, 2021

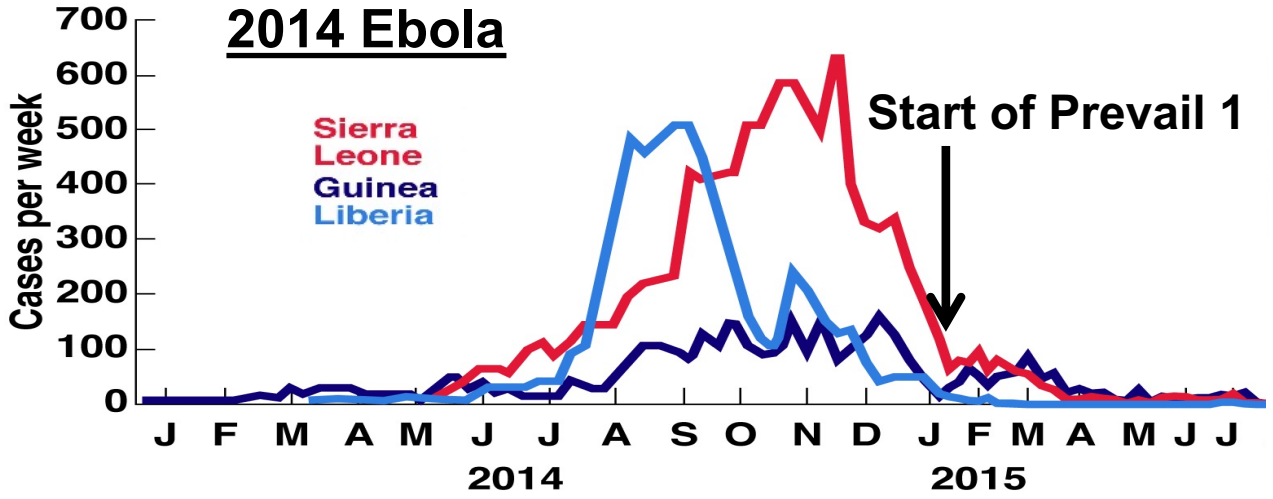
Outline – Part 1

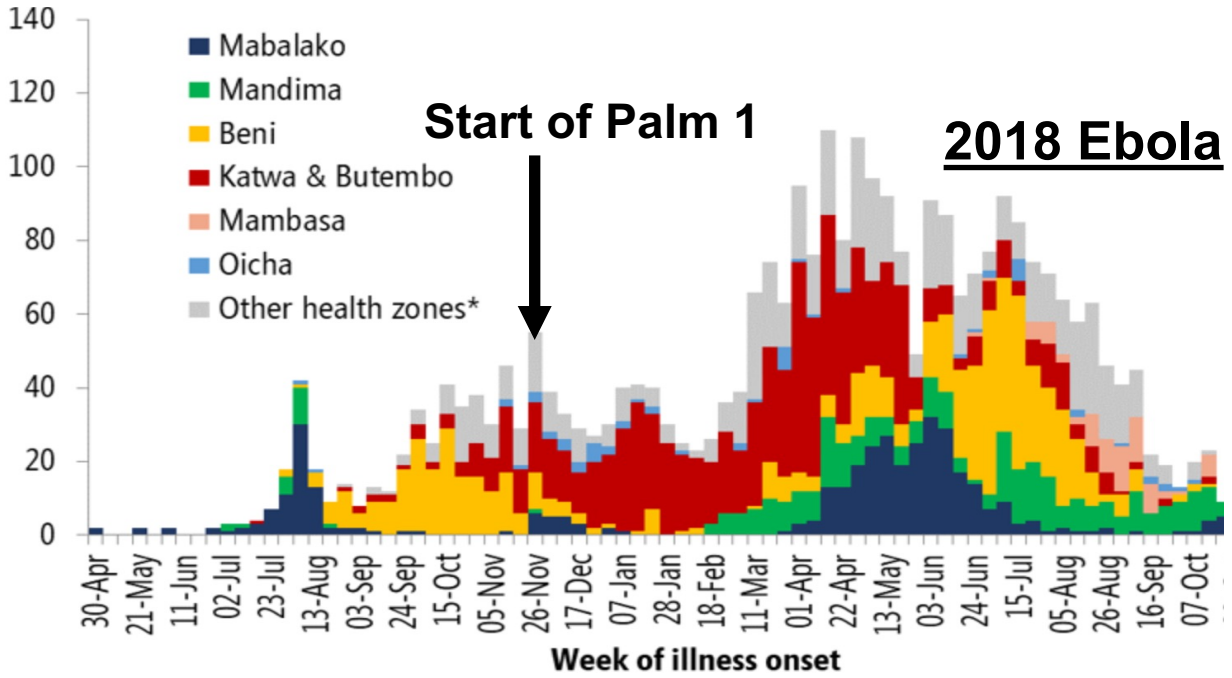
- Overview of completed and ongoing studies
  - ACTT
  - ACTIV
  - ACTIV-associated
- NIH Treatment Guidelines

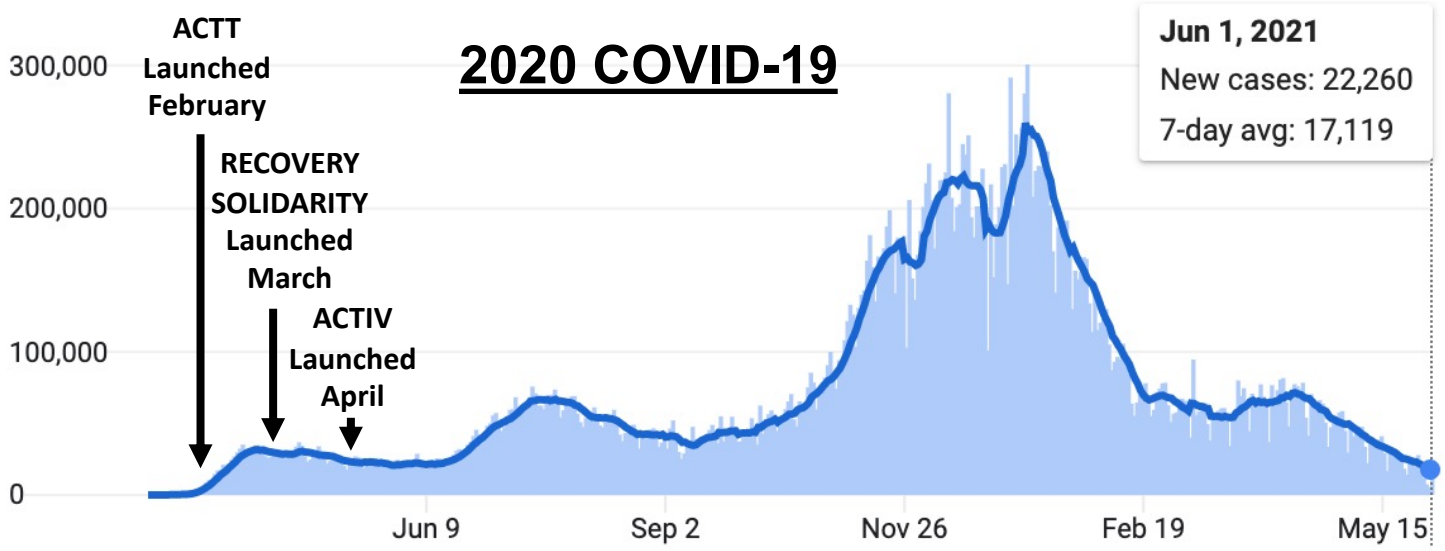
Large, Platform Trials Were Launched Early in the COVID-19 Pandemic



Progressively Rapid Initiation of RCTs During Outbreaks







Different Stages of COVID-19 Illness

COVID-19+ Disease Progression

No Symptoms → Outpatient, Mild Symptoms → Inpatient, No Oxygen → Inpatient, Low-flow Oxygen → Inpatient, High-flow Oxygen → Mechanical Ventilation

Anti-viral Strategies

Immunomodulatory Strategies

Anti-coagulation Strategies

The Adaptive COVID-19 Treatment Trial (ACTT; DMID/NIAID; John Beigel, PI)

- A randomized, controlled trial with an adaptive platform
- Eligibility: Adult patients hospitalized with COVID-19 and evidence of pulmonary disease
- Primary Endpoint: Time to recovery (ordinal scale 1, 2 or 3)
- Timeline: Study opened Feb. 21, 2020
- Has completed four versions; no immediate plans for a fifth
  - ACTT-1: Standard of care vs. remdesivir
  - ACTT-2: Remdesivir vs. remdesivir + baricitinib
  - ACTT-3: Remdesivir vs. remdesivir + interferon-β
  - ACTT-4: Dex + remdesivir vs. baricitinib + remdesivir

Top-Line Results from the ACTT Protocol

- Remdesivir superior to standard care with respect to shorter time to recovery (10 days vs. 15 days) with a trend toward lower 28-day mortality (11.4% vs. 15.2%)
  - Formed the basis of licensure for remdesivir
- Remdesivir + baricitinib superior to remdesivir alone with respect to time to recovery (7 days vs. 8 days) with a trend toward lower 28-day mortality (5.1% vs. 7.8%)
  - Led to an EUA for baricitinib
- Remdesivir + interferon beta-1a not superior to remdesivir alone
- Remdesivir + baricitinib not superior to remdesivir + dexamethasone

National Institutes of Health
Turning Discovery Into Health

Friday, April 17, 2020

News Release

NIH to Launch Public-Private Partnership to Speed COVID-19 Vaccine and Treatment Options

- The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership will:
  - Standardize and share preclinical evaluation methods in an open forum
  - Prioritize and accelerate clinical evaluation of therapeutic candidates with near-term potential
  - Maximize clinical trial capacity and effectiveness
  - Advance vaccine development

The ACTIV Public-Private Partnership Includes an Array of Industry and Government Organizations

INDUSTRY LEADERS

NOVARTIS	Eric Hughes John Tsai	Takeda	Rajeev Venkayya
Roche	John Young William Pao	SANOFI	(John Reed)
MERCK	Dean Li Betsy Desrosiers	J&J	Paul Stoffels
Pfizer	Mikael Dolsten Kathrin Jansen	Bristol Myers Squibb	Rupert Vessey Robert Plenge
RHYTHM THERAPEUTICS	David Meeker	VIR	Skip Virgin
AstraZeneca	(Mene Pangalos) Hitesh Pandya	Lilly	Dan Skovronsky
abbvie	Tom Hudson	GILEAD	Tomas Cihlar
Eisai	Lynn Kramer	dewpointx	Kara Carter
AMGEN	David Reese	gsk	John Lepore
NOVAVAX	Stan Erck	moderna	(Stéphane Bancel)

GOVERNMENT LEADERS

NIH National Institutes of Health *Turning Discovery Into Health*	Francis Collins Larry Tabak
NIH National Center for Advancing Translational Sciences	Joni Rutter Christine Colvis Mike Kurilla
NIH National Institute of Allergy and Infectious Diseases	(Anthony Fauci) Alan Embry Sarah Read Cliff Lane John Mascola Emily Erbelding
NIH NATIONAL CANCER INSTITUTE	Doug Lowy
NIH National Heart, Lung, and Blood Institute	Gary Gibbons
WHITE HOUSE COVID RESPONSE	David Kessler
BARDA Biomedical Advance Research and Development Authority	Gary Disbrow Robert Johnson
FDA	(Janet Woodcock) Peter Marks Peter Stein
EUROPEAN MEDICINES AGENCY	Marco Cavaleri
CDC	Barbara Mahon
VA U.S. Department of Veterans Affairs	Victoria Davey
U.S. Army MEDICAL RESEARCH AND DEVELOPMENT COMMAND	Brig. Gen. Michael Talley

NON-PROFIT

FNIH Foundation for the National Institutes of Health	Maria Freire (Steve Paul)
RTI INTERNATIONAL	Doris Rouse
FRED HUTCH CURES START HERE™	Larry Corey

PROGRAM MANAGEMENT

FNIH Foundation for the National Institutes of Health	David Wholley Joe Menetski Stacey Adam Michael Santos Stephanie James Margaret Anderson Nina Gonzalez Helen Chen Sarah Connelly Serena Melton Harrison Hawk Alex Cwalina Alex Sorosa Brett Tolman Jonathan Wachtel

Organizational Structure of ACTIV

- Co-Chairs: Francis Collins (NIH) and Paul Stoffels (JnJ)
- Executive Committee
  - USG: Tony Fauci (NIAID), Gary Gibbons (NHLBI), Peter Marks (FDA), Janet Woodcock (FDA), Gary Disbrow (BARDA)
  - Industry: Mikael Dolstein (Pfizer), William Pao (Takeda), Rajeev Venkayya (Takeda)
- Broken into four teams:
  - Preclinical (includes public database of variants)
  - Therapeutics (ACTIV 1-6 and ACTIV-associated trials)
  - Clinical Trial Capacity (retired)
  - Vaccines (forum for discussion of critical issues)

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Trials

- ACTIV-1 (NCATS): Immunomodulators in hospitalized patients
- ACTIV-2 (DAIDS/NIAID): Adaptive, 2-stage trial in outpatients
- ACTIV-3 (DCR/NIAID): Adaptive, 2-stage trial in hospitalized patients
- ACTIV-4 (NHLBI): Studies of anti-coagulation strategies
- ACTIV-5 (NIAID): Smaller sample sizes looking for a big effect
- ACTIV-6 (NCATS): Simple, adaptive trial in outpatients

ACTIV - Associated Trials

- ITAC – A randomized, controlled trial of immune IVIg in hospitalized patients (NIAID)
- OTAC – A randomized, controlled trial of immune IVIg in outpatients (NIAID)
- C3PO - Convalescent Plasma in Outpatients with COVID-19 (NHLBI)
- CONTAIN COVID-19 – Convalescent Plasma in Hospitalized Patients with COVID-19 (NCATS)

Findings from the ACTIV Family of Trials (1)

- Neither the monoclonal antibody bamlanivimab, VIR-7831, nor the combination of BRII-196 and BRII-198 passed initial futility parameters in hospitalized patients receiving remdesivir (ACTIV-3, NIAID).
- Immune IVIg + remdesivir was not superior to remdesivir alone in ordinal outcome at day 7 in hospitalized patients (ITAC, NIAID).
- Convalescent plasma was not superior to placebo in patients presenting to the ER with symptomatic COVID-19 (C3PO, NHLBI).

Findings from the ACTIV Family of Trials (2)

- In combination with data from the REMAP-CAP and ATTAC groups, the ACTIV-4 (NHLBI/CONNECTS) study found that:
  - Full dose anti-coagulation was superior to prophylactic dose anti-coagulation in reducing the need for vital organ support in moderately ill hospitalized patients.
  - Full dose anti-coagulation did not reduce the need for organ support in severely ill (ICU) hospitalized patients.

Current and Planned Agents Under Study in ACTIV

- Antivirals
  - Monoclonal antibodies AZD 7442/8895/7621; Brii 196/198; SAB 185; BMS 986413/14
  - Inhaled interferon-beta
  - Camostat (serine protease inhibitor)
- Oral anticoagulants
- Oral re-purposed agents
- Immunomodulators
  - Cencriviroc (CCR2/5 inhibitor)
  - Abatacept (Sol. CTLA-4)
  - Infliximab (anti-TNF)
  - Lensilumab (anti-GM-CSF)
  - Risankizumab (anti-IL23)

A June 3, 2021 Search of ClinicalTrials.gov Revealed 3,652 Different Studies

National Institutes of Health
Turning Discovery Into Health

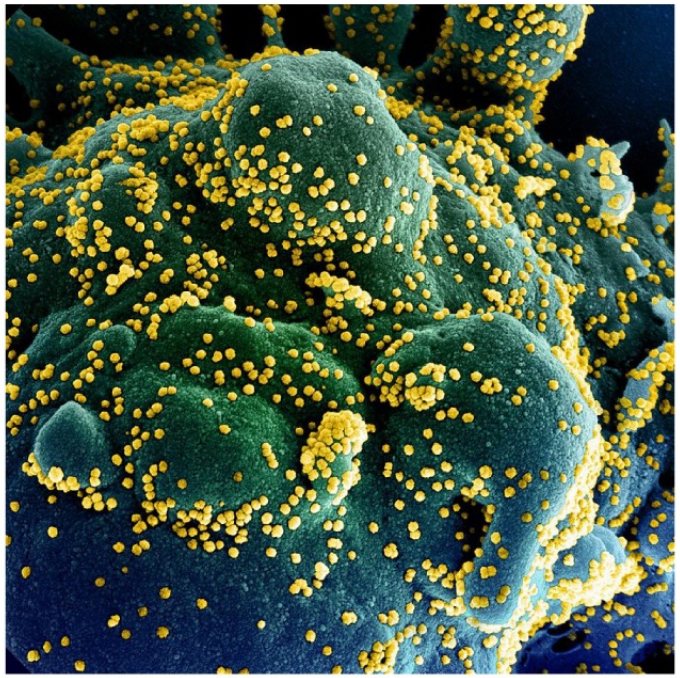
Tuesday, April 21, 2020

News Release

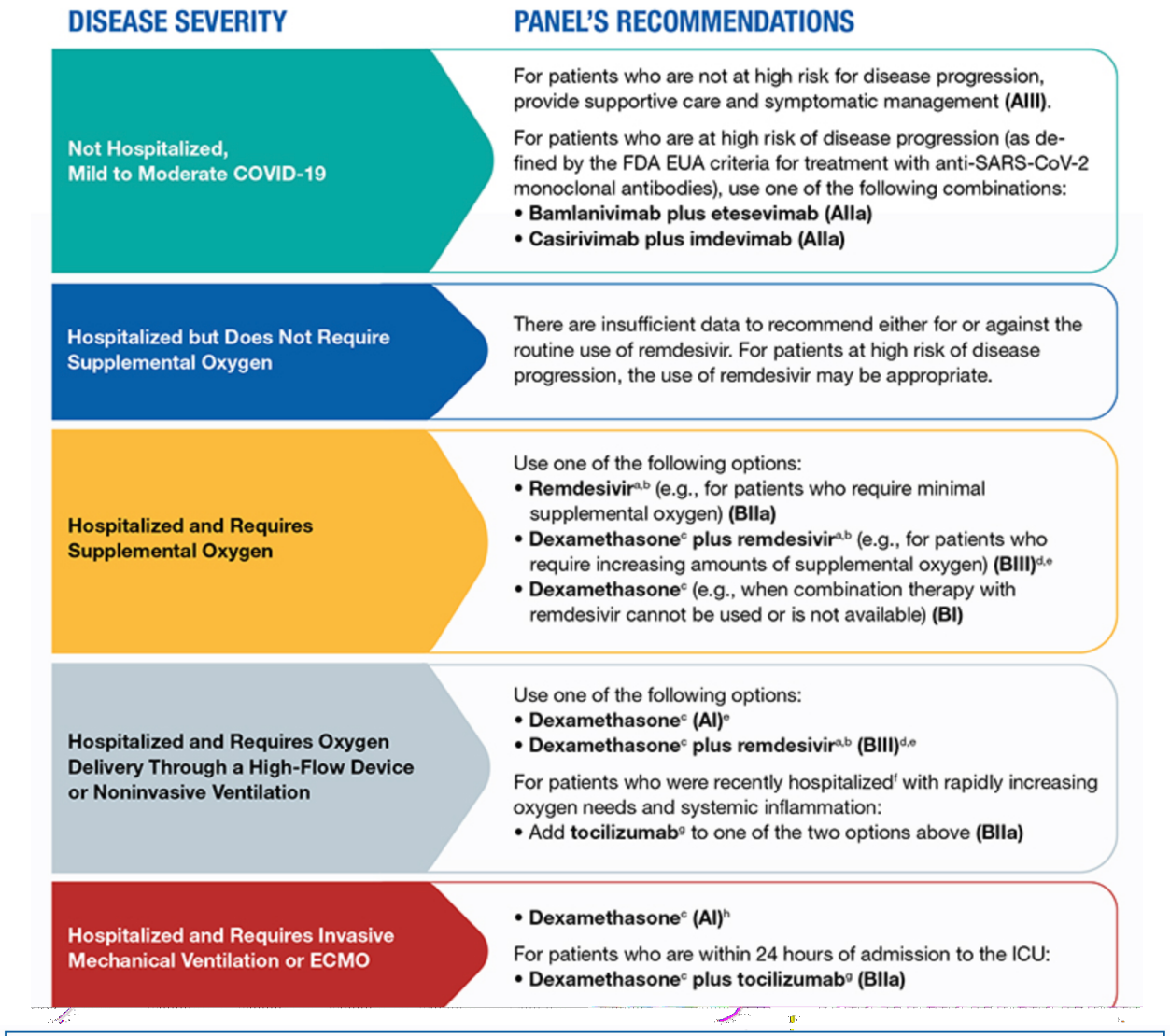
Expert U.S. Panel Develops NIH Treatment Guidelines for COVID-19

"Living document" expected to be updated often as new clinical data accrue

- **Covid19treatmentguidelines.nih.gov**



NIH Treatment Guidelines Panel Recommendations for Treatment of COVID-19



DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	For patients who are not at high risk for disease progression, provide supportive care and symptomatic management **(AIII)**. For patients who are at high risk of disease progression (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations: • **Bamlanivimab plus etesevimab (AIIa)** • **Casirivimab plus imdevimab (AIIa)**
Hospitalized but Does Not Require Supplemental Oxygen	There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[a,b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[c] **plus remdesivir**[a,b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[d,e] • **Dexamethasone**[c] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[c] **(AI)**[e] • **Dexamethasone**[c] **plus remdesivir**[a,b] **(BIII)**[d,e] For patients who were recently hospitalized[f] with rapidly increasing oxygen needs and systemic inflammation: • Add **tocilizumab**[g] to one of the two options above **(BIIa)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	• **Dexamethasone**[c] **(AI)**[h] For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[c] **plus tocilizumab**[g] **(BIIa)**

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

- March 20 – request from HHS
- March 22 – initial 37 members identified; 6 USG agencies; 8 professional societies
- March 24 – first meeting
- April 7 – first release ready
- April 21 – final approval
- Since then:
  - 25 major revisions
  - 17,377,931 page views